REMARKS

The Advisory Action of June 16, 2002 states that the amendments submitted in the Response to the final Office Action were not entered. Therefore, the current amendments are based on the amendments of August 7, 2001.

Claims 18-34 are pending. New Claims 35 and 36 are added. Claims 18-29 are amended to correct obvious typographical errors. Claims 18 and 29 are further amended for technical clarity. Support is found throughout the specification, for example, at page 4, line 10 to page 5, line 7. Support for new Claims 35 and 36 is found throughout the specification, for example, at page 1, lines 1 and 9; and page 4, lines 10-34. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE". An appendix of the pending claims is attached for the Examiner's convenience.

New matter has not been added by way of these amendments and the Examiner is respectfully requested to enter them. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow

Rejection under 35 U.S.C. § 102(e):

Claims 18, 20, 22, 23, and 29-32 stand rejected under 35 U.S.C. § 102(e) as being anticipated by the microsphere-based analytical chemistry system disclosed by Walt *et al.* in U.S. Patent No. 6,023,540. The Examiner contends that the disclosure by Walt *et al.* of "groups of fibers", "individual fibers", and an "optical fiber bundle" anticipate, respectively, the claimed "plurality of array locations", a "plurality of discrete sites", and a "plurality of assay locations". Applicants respectfully traverse.

Walt *et al.* disclose "an optical fiber bundle sensor in which separate beads or microspheres may be optically coupled to discrete fibers or groups of fibers within the bundle" (*see* column 3, lines 23-25).

In contrast, the claimed invention employs a surface comprising a plurality of assay locations, wherein each assay location comprises an array location comprising a plurality of discrete cites.

M.P.E.P. § 2131 provides that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference[.]" *Veredegaal Bros. v. Union Oil Co. of California*, 84 F.2d 628 (Fed. Cir. 1987). In

view of this standard, Applicants respectfully assert that Walt *et al.* do not anticipate the substrate of Claim 18 which comprises a plurality of assay locations, each comprising an array location comprising discrete sites.

Applicants submit that the "groups of fibers" disclosed by Walt *et al.* rather than anticipating the claimed plurality of array locations is an alternative means for detecting the light emitted from an individual microsphere. Walt *et al.* describe optical coupling and means for detecting the light emitted from a microsphere at column 3, lines 23-25. Walt *et al.* state that a microsphere is either optically coupled to a discrete fiber within a bundle or is optically coupled to more than one fiber, *i.e.*, "groups of fibers", within a bundle. Walt *et al.* further state in Claim 9: "light from individual bead being coupled into separate or groups of separate fibers of the bundle for transmission to the proximal end of the bundle" (*see* column 16, lines 18-29). Thus, Applicants submit that "groups of fibers" as defined by Walt *et al.* is not a plurality of array locations but rather is a means for detecting the light emitted from an individual microsphere.

In view of the definition of "groups of fibers", Applicants submit that the "optical fiber bundle" of Walt *et al.* does not anticipate the claimed plurality of assay locations. Applicants' position is based on the interrelatedness of the claimed assay and array locations. As recited in Claim 18, each assay location comprises an array location. Therefore, in the absence of the claimed array locations there can be no plurality of assay locations as presently claimed. Applying this reasoning to Walt *et al.*, Applicants submit as set forth above that the "groups of fibers" of Walt *et al.* do not anticipate the claimed array locations; therefore, logic dictates that the "optical fiber bundle" of Walt *et al.* does not comprise a plurality of array locations and does not anticipate the claimed plurality of assay locations.

Applicants respectfully assert that the rejection under 35 U.S.C. § 102(e) of Claim 18, 20, 22, 23, and 29-32 is improper and request that it be withdrawn.

Rejection under 35 U.S.C. § 103(a):

Claims 18-32 stand rejected as being unpatentable over Walt *et al.*, U.S. Patent No. 6,023,540; Geyson, U.S. Patent No. 5,595,915; and Brenner, U.S. Patent No. 5,763,175. Claims 33 and 34 stand rejected over Walt *et al.* The Examiner apparently contends that the combination of Walt *et al.*, Geyson, and Brenner establishes a *prima facie* case of obviousness because it would have been obvious to one of ordinary skill in the art at the time the invention was made to scale up the number of analytes that could be simultaneously screened. Applicants respectfully traverse.

Walt *et al.* describe a microsphere-based analytical chemistry system that includes an optical fiber bundle sensor in which separate microspheres are optionally coupled to fibers or groups of fibers (*see* column 3, lines 23-25).

Geyson describes a method of identifying antigenically active peptide sequences that employs peptides attached to rods optionally arranged in a grid having dimensions that may correspond to a microtiter plate (*see* column 3, lines 5-35). It is Applicants' understanding that the method of Geyson requires the use of a single, unique peptide on each rod. When used in this manner, a rod to which an antibody binds is indicative of an antigenically active peptide sequence attached thereto.

Brenner describes a method of sequencing a population of polynucleotides that employs a spatially addressable array of tag complements.

M.P.E.P § 2142 states that a combination of prior art references does not support a § 103(a) rejection unless "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success [are] both found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." M.P.E.P. § 2143.01 continues, stating that "the prior art must suggest the desirability of the claimed invention" and "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990)[.]" Recently, the Federal Circuit overturned the Board of Patent Appeals and Interferences' ("Board's") decision to uphold a § 103(a) rejection because "the Board rejected the need for 'any specific hint or suggestion in a particular reference' to support the combination. . . of references." *In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002). The court concluded: "Omission of a relevant factor required by precedent is. . . legal error[.]" *Id.*

In view of this standard, Applicants submit that the Examiner's rejection based on the proposition that a skilled artisan would arrive at the claimed invention from a motivation to improve screening efficiency is improper. Even assuming *arguendo* that a skilled artisan is motivated to increase the efficiency of an assay, the Examiner's position does not support the conclusion that the references are properly combined to arrive at the claimed invention. The Examiner's position does not meet the requirement that the prior art references teach or suggest all the claim limitations, that the references or the general knowledge of a skilled artisan provide a suggestion or motivation to modify the references or combine reference teachings, and that there is a reasonable expectation of success. M.P.E.P. § 2143.

During the prosecution of the subject application, the Examiner has not been persuaded by the arguments provided above. Rather, the Examiner maintained the obviousness rejection because Applicants did not rebut the alleged motivation of a skilled artisan to improve assay efficiency and because Applicants restricted their arguments to the context of the claimed invention. As stated by the Examiner in the Office Action of October 19, 2001:

> Applicant does not appear to argue that one of ordinary skill in the art would not have been motivated in increase [sic] the number of analytes screened for. Applicant appears to argue that one of ordinary skill in the art would not have been motivated to scale up the number of analytes screened for using the presently claimed method.

In view of the Examiner's comment, Applicants submit that the Examiner's reasoning in making the rejection and his rebuttal to Applicants' response to the rejection are improper. Legal precedent and the M.P.E.P. state that arguments for and against patentability are to be framed within the context of the claimed invention. The Federal Circuit commenting on the proper form of a § 103(a) rejection stated that "particular findings must be made as to the reason the skilled artisan, with no knowledge of the *claimed invention*, would have selected these components for combination in the manner *claimed*." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) (emphasis added). The court also has found that "the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the *claimed invention* obvious." *In re Fitch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (emphasis added). M.P.E.P. § 2143 provides that references when combined must teach or suggest all the *claim* limitations (emphasis added). "The teaching or suggestion to make the *claimed* combination and the reasonable expectation of success must both be found in the prior art[.]" M.P.E.P.§ 2141 (emphasis added). Therefore, the Examiner's position regarding a skilled artisan's motivation does not properly address the requirement that the references be combined in a manner that meets the legal standard of obviousness.

The Examiner has stated further that certain aspects of the claimed invention (*e.g.*, microtiter plates) were "routine, if not standard, in the art at the time the invention was made" (*see* Office Action, October 19, 2001). This statement suggests that the Examiner is relying on the level of skill in the art to establish a rationale for combining prior art references; however, this too is improper. The M.P.E.P. states "[t]he level of skill in the art cannot be relied upon to provide the suggestion to combine references." § 2143.01 (citing *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999).)

Applicants maintain that Walt *et al.*, Geyson, and Brenner do not render the claimed invention obvious. For the reasons stated in the Responses of April 16, 2002 and August 7, 2001, the references alone or in combination do not establish a *prima facie* case of obviousness. Applicants respectfully request the Examiner to reconsider Applicants remarks set forth in these responses in view of the remarks provided herein and respectfully request the rejection under § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner believes there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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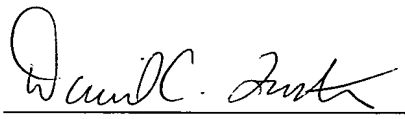

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 18-29 are amended as follows:

18. (Twice Amended) A method of determining the presence of one or more target analytes in one or more samples comprising:

a) contacting said one or more samples~~sample~~ with a composition comprising:

i) a substrate with a surface comprising a plurality of assay locations, each assay location comprising an array location comprising a plurality of discrete sites; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent~~,~~; wherein said microspheres are distributed on said surface such that said discrete sites each contain no more than one microsphere; and

b) determining the presence or absence of said target analyte.

19. (Twice Amended) A method of determining the presence of one or more target analytes in one or more samples comprising:

a) adding said one or more samples~~sample~~ to a first substrate comprising a plurality of assay locations, such that said sample is contained at a plurality of said assay locations;

b) contacting said sample with a second substrate comprising:

i) ~~a surface comprising~~ a plurality of array locations, each array location comprising a plurality of discrete sites, wherein at least one assay location is in fluid contact with at least one array location; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent~~,~~; wherein said microspheres are distributed on at least one of said array locations~~surface~~ such that said discrete sites each contain no more than one microsphere; and

c) determining the presence or absence of said target analyte.

20. (Twice Amended) A method according to claim 18~~,~~ wherein each of said assay locations comprises a library of bioactive agents.

21. (Amended) A method according to claim 18, wherein said substrate is a microtiter plate and each assay location is a microtiter well.

22. (Amended) A method according to claim 18, wherein each discrete site is a bead well.

23. (Amended) A method according to claim 18, wherein each of said subpopulations further comprise an optical signature capable of identifying said bioactive agent.

24. (Twice Amended) A method according to claim 18, wherein at least a first and second microsphere in said subpopulations further comprise an identifier binding ligand that will bind a decoder binding ligand, whereby said bioactive agent is identified by said identifier binding ligand binding to said decoder binding ligand.

25. (Amended) A method according to claim 19, wherein said first substrate is a microtiter plate.

26. (Amended) A method according to claim 19 or 25, wherein said second substrate comprises a plurality of fiber optic bundles comprising a plurality of individual fibers, each bundle comprising an array location, and each individual fiber comprising a bead well.

27. (Amended) A method according to claim 19, wherein each of said subpopulations further comprise an optical signature capable of identifying said bioactive agent.

28. (Amended) A method according to claim 19, wherein each of said subpopulations further comprise an identifier binding ligand that will bind a decoder binding ligand such that the identification of the bioactive agent can be elucidated.

29. (Amended) A method according to claim 18 or 19, wherein at least one of said target analytes is a nucleic acid.

Claims 35 and 36 are added as follows:

--35. (New) A method of determining the presence of one or more target analytes in one or more samples comprising:

a) contacting said one or more samples with a composition comprising:

i) a composite array comprising a plurality of assay locations, each assay location comprising an array location comprising a plurality of discrete sites; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent, wherein said microspheres are distributed on said surface such that said discrete sites each contain no more than one microsphere; and

b) determining the presence or absence of said target analyte.

36. (New) A method of determining the presence of one or more target analytes in one or more samples comprising:

a) adding said one or more samples to a first substrate comprising a plurality of assay locations, such that said sample is contained at a plurality of said assay locations;

b) contacting said sample with a second substrate comprising:

i) a composite array comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein at least one assay location is in fluid contact with at least one array location; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent, wherein said microspheres are distributed on said surface such that said discrete sites each contain no more than one microsphere; and

c) determining the presence or absence of said target analyte.--